Advances in diagnosis and treatment of tubal subfertility

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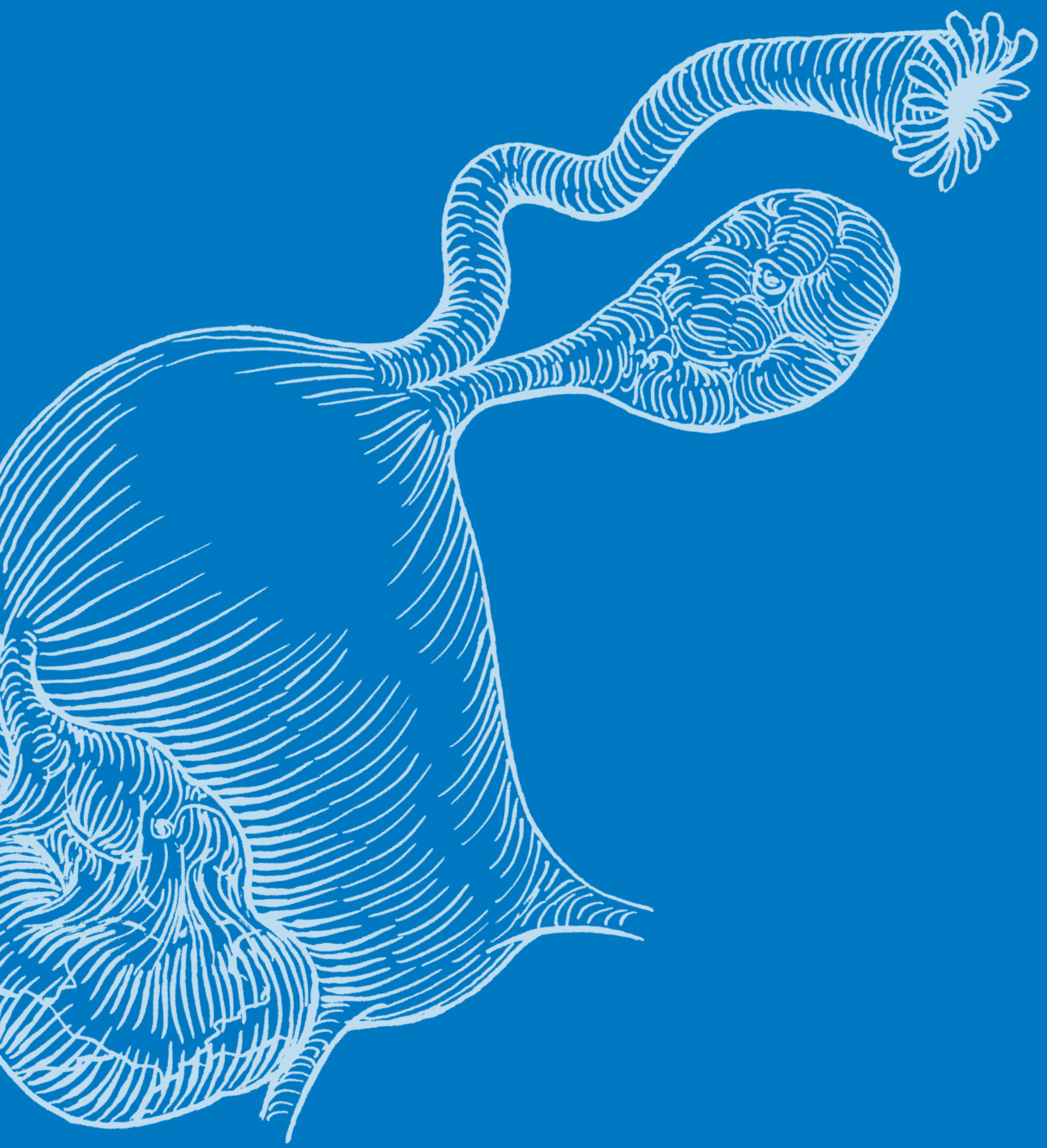

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General introduction and outline of this thesis

GENERAL INTRODUCTION

Reinier de Graaf (1641-1673) was a Dutch physician and anatomist who may have been the first who understood and described the function of the Fallopian tubes. Although the Fallopian tubes were named after Gabriele Falloppio (1523-1562), who described the anatomy of these female organs for the first time, Reinier de Graaf was the first to discover their true function. These tubes, also known as salpinges, facilitate the transport of sperm cells from the uterus to the distal part of the tubes, and conversely of the oocyte and embryo from the distal part to the uterus. Fallopian tubes can be divided into different parts: the intramural segment, the isthmus, the ampulla and the infundibulum with its fimbrial end (Figure 1).[1,2]

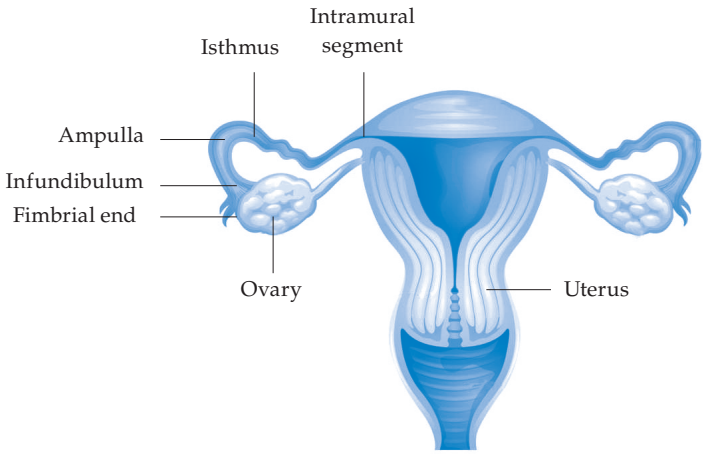

Figure 1: *Uterus and Fallopian tubes*

The infundibulum picks-up the ovulated egg with the fimbrial end, and facilitates the entrance of the oocyte into the ampulla. The sperm cells, which enter the uterus by the vagina and the cervix, swim from the intramural segment through the Fallopian tubes to the ampulla were they meet the oocyte and where fertilization can occur, with the growth of an embryo as result. The epithelium of the ampulla contains ciliated and non-ciliated cells. The ciliated cells facilitate the transport of the embryo from the ampulla through the isthmus and intramural segment into the uterus, together by peristaltic contractions of the tubal wall. The non-ciliated cells produce tubal fluid, containing nutrients that influence the embryo development. The production of tubal fluid changes during the menstrual cycle with the highest

production around the time of ovulation. When the embryo enters the uterus, implantation in the endometrium will take place and the pregnancy can further develop.

TUBAL SUBFERTILITY

Subfertility is defined as the inability to conceive within one year of unprotected intercourse.[3] It affects approximately one out of ten couples trying to get pregnant.[4] In the Netherlands about 50.000 couples consult a general practitioner because of subfertility each year and 30.000 of these couples visit a gynaecologist.[5] One of the most common types of subfertility is tubal subfertility, with an incidence of 15-30%.[6] Tubal subfertility is the result of injury to the Fallopian tubes, called tubal pathology. The three most common causes of tubal pathology and thus tubal subfertility, are pelvic inflammatory diseases (PID), endometriosis and injury due to surgical procedures.[1]

Tubal pathology can be classified as proximal or distal. Proximal tubal pathology concerns injury to the intramural segment or isthmus of the Fallopian tube. This form is seen in 20-25% of women with tubal subfertility. Pathology of the ampulla, infundibulum or fimbriae is called distal tubal pathology and affects 70-90% of women with tubal subfertility.[1] When the fimbrial end of the tube is completely occluded, fluid produced by the non-ciliated cells will collect in the distal part of the tube leading to distension. This form of tubal pathology is called a hydrosalpinx and represents the most severe form of distal tubal pathology.

DIAGNOSIS OF TUBAL SUBFERTILITY

As part of a standard evaluation of subfertility, which generally includes an assessment of the (ovulatory) cycle and a semen analysis, the patency of the Fallopian tubes is assessed.[5] This evaluation of tubal patency can be done by several different tests, including hysterosalpingography (HSG), Rubin's test (not in use anymore), diagnostic laparoscopy and hysterosalpingo sonography. Each of these tests has different diagnostic and therapeutic options, potential complications and costs, but all of them are primarily used to evaluate the patency of the Fallopian tubes.

Hysterosalpingography (HSG) is one of the oldest tubal patency tests, and is still commonly used in the Netherlands.[6] With HSG a radiopaque contrast medium is infused through the cervix into the uterine cavity and subsequently into the

Fallopian tubes. During infusion of the contrast radiographs (X-ray's) are made to evaluate the shape of the uterine cavity and the patency of the Fallopian tubes.[7] The technique of HSG has hardly changed over the years. However, the type of contrast medium to be used has constantly been subject of debate. The HSG procedure was first describes in 1910 by Rindfleisch using injection of a bismuth solution, although he only evaluated the uterine cavity.[8] Cary was the first who described the evaluation of tubal patency by the HSG procedure in 1914, with Collergol® as radiopaque contrast medium.[9] However, since Collergol® was found to potentially cause serious adverse events like peritonitis and severe pain, HSG was abandoned for several years.[10] Some 10 years later HSG was re-introduced with the use of an oil-based contrast medium: Lipiodol®. Lipiodol® seemed to offer a save alternative to Collergol®. However, Lipiodol® was subsequently gradually replaced by different water-based contrast media in most clinics. Reasons were lower costs, better imaging of the ampulla and a lower likelihood of complications such as anaphylaxis or lipogranuloma formation.

Another aspect of HSG that has been subject of debate for many years, is the potential therapeutic effect of an HSG. Although initially introduced as a diagnostic test, HSG is suggested to lead to an increase in pregnancy rate.[11] However, high-quality evidence supporting this theory is lacking. Furthermore, it is unclear whether the choice of contrast medium used during HSG affects this potential therapeutic effect.[12]

In 1920, while the HSG procedure with use of Collergol® was abandoned, Rubin introduced an alternative method to evaluate tubal patency, also known as Rubin's test.[13] With Rubin's test, gas is insufflated through the cervix into the uterine cavity. Subsequently, trans tubal passage of gas, and thus tubal patency, is assessed by listening with a stethoscope for gas-bubbles escaping the tubal ends into the abdominal cavity. Additionally, women are asked to stand up after the procedure to determine if referred shoulder pain is experienced from diaphragmatic irritation by the gas. Presence of intra-abdominal gas may also be demonstrated by X-ray or fluoroscopy. For his test, Rubin first used oxygen but later switched to carbon dioxide for insufflation, as carbon dioxide is absorbed more quickly and causes less pain.

Another way to assess tubal patency is by direct visualisation of the female genital tract. Until the late nineteen-forties this could only be done by laparotomy. The disadvantage of a laparotomy is the high risk of complications. Furthermore,

laparotomic surgery can induce intra-abdominal adhesions, which can lead to tubal pathology and tubal infertility as result. A less invasive surgical technique, laparoscopic surgery, was first performed in humans in 1910 by the Swedish internist Hans Christian Jacobaeus. During the ensuing decades, numerous individuals refined and popularized this surgical approach. It was until 1947 when Raoul Palmer, a French gynaecologist, was the first who published on diagnostic laparoscopy for evaluation of the internal female genital tract. Palmer used a cystoscope to directly observe the female genital organs trans-abdominally. Specific evaluation of tubal patency using diagnostic laparoscopy was first done in the mid-1980s, when chromopertubation was added to the procedure. With chromopertubation a contrast medium is infused through the cervix into the uterine cavity. Passage of contrast through the Fallopian tubes into the abdominal cavity is evaluated by direct visualisation with the laparoscope. Laparoscopy has the advantage over other tubal patency tests that it allows direct visualisation of the whole female internal genital tract, and enables treatment during the same procedure in case of abnormal findings. Therefore, diagnostic laparoscopy is currently considered the gold standard test for evaluation of tubal patency, although it is an invasive procedure and carries more risks compared to the other tubal patency tests.[6]

The most recent development in tubal patency testing is based on transvaginal ultrasound examination of the Fallopian tubes. Ultrasound is a commonly used imaging technique in gynaecology and reproductive medicine. It has the advantages of being save and minimally invasive. Since the introduction of the transvaginal ultrasound in the mid-1980s, the imaging technique has been widely used for various diagnostic purposes. Initially the ultrasound was used to evaluate the ovaries in women undergoing fertility treatments. As the imaging quality improved, evaluation of other parts of the female internal genitals, like the uterus and cervix, became possible. Even the formation of hydrosalpinges could now be diagnosed by ultrasound examination.[14] This raised the question if evaluation of tubal patency could also be done by this diagnostic technique. Deichter was the first to do so in 1986, and introduced the sonographic tubal patency test Hysterosalpingocontrast sonography (HyCoSy).[15-17] During HyCoSy an echogenic contract medium (Echovist®) is infused into the uterine cavity. At the same time a transvaginal ultrasound examination is performed to examine the uterus and uterine cavity, and to observe whether or not flow of contrast is seen through the Fallopian tubes. In contrast to HSG, the ovaries can also be evaluated during this test. The HyCoSy has been suggested to offer a less invasive alternative to HSG (no X-ray) and diagnostic laparoscopy (no

surgery). The accuracy of HyCoSy was shown to be comparable to or even better than HSG in predicting tubal patency.[18-21] However, the required echogenic medium for HyCoSy, Echovist®, was found to potentially cause allergic reactions and its use for sonographic tubal patency testing was stopped. In 1995 Heikkinen developed an alternative medium for sonographic tubal patency testing, using air mixed in saline instead of Echovist®.[22] A disadvantage of this contrast medium is that the air bubbles rapidly disappear from the saline, requiring a very quick evaluation of the tubal status. Therefore, Exalto and Emanuel developed a more stable medium for sonographic tubal patency testing in 2011: echogenic Foam. This echogenic Foam is created by rigorously mixing 10 cc ExEm-gel® with 10 cc of purified water in a 20 cc syringe. The created Foam is stable for approximately 5 minutes and fluidly enough to pass through patent tubes. By replacing Echovist® or air in saline by this echogenic Foam, the resulting hysterosalpingo-foam sonography (HyFoSy) offered a new minimal invasive technique for tubal patency testing.[23;24]

TREATMENT OF TUBAL SUBFERTILITY

The location and the severity of tubal pathology determine the best treatment option. In vitro fertilisation (IVF) is the best treatment in case of proximal tubal pathology, severe tubal pathology, or a combined proximal and distal tubal pathology. However for women with isolated distal tubal pathology there are also surgical options besides IVF. For example, a narrowing of the distal end of the Fallopian tube, called phimosis, can be surgical corrected by a fimbrioplasty. Adhesions at the outside of the Fallopian tube, leading to reduced motility of the tube or narrowing or occlusion of the tubal lumen, can be treated by a laparoscopic adhesiolysis (removal of the adhesions).

As aforementioned, the most severe form of tubal subfertility is a hydrosalpinx. Women with hydrosalpinges are often designated to IVF to become pregnant. However, the presence of hydrosalpinges during IVF treatment has been found to markedly reduce pregnancy outcomes following IVF treatment with almost 50%.[25;26] There are several theories explaining the negative influence of hydrosalpinges on IVF outcomes. The most common theory is that the collected tubal fluid may leak into the uterine cavity and can washout a transferred embryo.[27-29] The presence of hydrosalpingeal fluid in the uterine cavity is also suggested to have a detrimental influence on endometrial receptivity, thereby impairing the implantation potential.[30-32] Embryo toxicity of hydrosalpingeal fluid has also been suggested as

cause for the reduced pregnancy outcome following IVF.[33] Because of the negative influence, subfertile women with hydrosalpinges need to be treated to increase their pregnancy chances before they start IVF. Various interventions have been studied as treatment for hydrosalpinges.[34] All are based on blocking or reducing the flow of hydrosalpinx fluid towards the uterine cavity. Possible interventions include laparoscopic salpingectomy (surgical removal of the whole Fallopian tube), salpingostomy (opening the distended distal part of the hydrosalpinx), proximal tubal ligation (occluding the proximal part of the Fallopian tube during laparoscopy by cauterisation) and transvaginal aspiration of hydrosalpingeal fluid. Laparoscopic salpingectomy is currently considered the standard treatment and is found to increase ongoing pregnancy rates following IVF by almost 50% compared to no intervention.[34] However, laparoscopic salpingectomy is invasive and carries anesthesiological and surgical risks. Alternative less invasive treatment options for subfertile women with hydrosalpinges are therefore needed. A potential effective and less invasive alternative treatment option is proximal tubal occlusion by hysteroscopic placement of Essure® devices.[25;26;35-44] However, further research is needed to evaluate the effectivity of this new treatment.

AIM OF THIS THESIS

The aim of this thesis was to answer the following questions:

Does tubal patency testing by hysterosalpingography (HSG) increase ongoing pregnancy rates in couples with unexplained subfertility undergoing the routine fertility work-up?

Does tubal flushing during HSG, as part of the basic fertility work-up, with an oil-based contrast medium leads to higher ongoing pregnancy rates within six months compared to the use of water-based contrast medium?

Is hysterosalpingo-foam sonography (HyFoSy) a less painful procedure compared to serial hysterosalpingography (HSG) as a first line tubal patency test during the basic fertility work-up?

Is hysterosalpingo-foam sonography (HyFoSy) an accurate test to confirm proximal tubal occlusion after Essure® device placement as treatment for hydrosalpinges prior to IVF?

Does hysteroscopic proximal tubal occlusion by Essure® devices as treatment for hydrosalpinges result in comparable ongoing pregnancy rates following IVF/ICSI as compared to laparoscopic salpingectomy?

Has the presence of an Essure® intratubal device a negative influence on pregnancy outcome?

OUTLINE OF THIS THESIS

This thesis is divided into three parts. The first part focuses on the therapeutic effect of hysterosalpingography in subfertile women. The second part evaluates different aspects of the recently introduced sonographic tubal patency test; hysterosalpingo-foam sonography (HyFoSy). The third part describes a new less invasive treatment option for subfertile women with hydrosalpinges and the impact of this treatment on pregnancy outcomes after IVF/ICSI.

PART I – Therapeutic effect of diagnostic tubal patency testing

In Chapter 2 we evaluated the therapeutic effect of tubal patency testing by hysterosalpingography (HSG) during the basic fertility work-up. For this evaluation we performed a secondary analysis on a prospective cohort of 4547 subfertile women included between January 2002 and Februari 2004 in 38 hospitals in the Netherlands.

In Chapter 3 we compared the therapeutic effect of tubal flushing by HSG with an oil-based contrast medium versus a water-based contrast medium. This study was a nationwide randomised controlled trial in 27 clinics in the Netherlands that included 1119 subfertile couples. The primary outcome of this study was ongoing pregnancy at 6 months following HSG.

PART II – Sonographic tubal patency testing

In Chapter 4 we compared in a randomised controlled trial the pain experienced during a new sonographic tubal patency test: hysterosalpingofoam sonography (HyFoSy) and HSG. This study was a two-centre randomised controlled trial that included 40 patients. The primary outcome was pain scores during tubal patency testing measured by a Visual Analogue Scale (VAS).

In Chapter 5 we describe our prospective diagnostic accuracy study in which we evaluated if hysterosalpingo-foam sonography (HyFoSy) is even accurate as hystersosalpingography (HSG) to confirm proximal tubal occlusion after placement

of an Essure® device as treatment for a hydrosalpinx prior to IVF. In this study we evaluated 38 hydrosalpinges treated by Essure® devices in 26 women who participated in the DESH trial (Dutch Essure® versus Salpingectomy for Hydrosalpinges) (chapter 7).

PART III – Treatment of hydrosalpinges by Essure® devices

In Chapter 6 we evaluated the effectivity of hysteroscopic proximal tubal occlusion by Essure® devices in women with a relative contraindication for a laparoscopic salpingectomy, prior to the start of their IVF treatment. In this prospective clinical study we included 20 women.

In Chapter 7 we compared the effectivity of hysteroscopic Essure® device placement to laparoscopic salpingectomy as treatment for hydrosalpinges prior to start IVF. In this nationwide randomised clinical trial we included 85 women with ultrasound visible hydrosalpinges between 2009 and 2014. The primary outcome of this study was ongoing pregnancy rate following one IVF treatment cycle.

In Chapter 8 we evaluated the obstetrical outcomes of 50 pregnancies in 43 women who became pregnant with Essure® devices in situ before December 2010 in the Netherlands.

REFERENCES

1. Nap AdTKJ. Handboek voortplantings-geneeskunde. de Tijdstroom; 2013.
2. Strauss JFBRL. Yen and Jaffe's Reproductive Endocrinology; physiology, pathophysiology, and clinical management. Elsevier; 2015.
3. Zegers-Hochschild F, Adamson GD, de MJ, Ishihara O, Mansour R, Nygren K et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. Fertil Steril 2009; 92(5):1520-1524.
4. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod 2007; 22(6):1506-1512.
5. NVOG guideline. National guideline subfertility. Dutch guidelines for Obstetrics and Gynaecology. 2011.
6. NVOG guideline. National guideline basic fertility work up. Dutch guidelines for Obstetrics and Gynaecology. 2004.
7. Schoenmaker J. Seriehysterosalpingografie. Thesis [1973.
8. Rindfleisch.W. Darstellung des cavum uteri. Klin Wochenscher 1910; 47:780.
9. Classic pages in Obstetrics and Gynecology. Note on determination of patency of Fallopian tubes by the use of collargol and x-ray shadow. By William Hollenback Cary. American Journal of Obstetrics and Diseases of Women and Children, vol. 69, pp. 462-464, 1914. Am J Obstet Gynecol 1973; 117(7):1001.
10. Hanlo E.A.J.M. Uterosalpingographie. Thesis [1930.
11. Cundiff G, Carr BR, Marshburn PB. Infertile couples with a normal hysterosalpingogram. Reproductive outcome and its relationship to clinical and laparoscopic findings. J Reprod Med 1995; 40(1):19-24.
12. Mohiyiddeen L, Hardiman A, Fitzgerald C, Hughes E, Mol BW, Johnson N et al. Tubal flushing for subfertility. Cochrane Database Syst Rev 2015; 5:CD003718.
13. Rubin IC. Landmark article Sept. 4, 1920: The nonoperative determination of patency of fallopian tubes by means of intra-uterine inflation with oxygen and the production of an artificial penumoperitoneum. By I.C.Rubin. JAMA 1983; 250(17):2359-2365.
14. Patel MD, Acord DL, Young SW. Likelihood ratio of sonographic findings in discriminating hydrosalpinx from other adnexal masses. AJR Am J Roentgenol 2006; 186(4):1033-1038.
15. Deichert U, van de Sandt M, Lauth G, Daume E. [Transvaginal contrast hysterosonography. A new diagnostic procedure for the differentiation of intrauterine and myometrial findings]. Geburtshilfe Frauenheilkd 1988; 48(12):835-844.
16. Deichert U, Schlief R, van de Sandt M, Gobel R, Daume E. [Transvaginal contrast hysterosalpingo-sonography with the B-image procedure and color-coded duplex sonography for the assessment of fallopian tube patency]. Geburtshilfe Frauenheilkd 1990; 50(9):717-721.
17. Deichert U. [Contrast hysterosalpingography (or HyCoSy)]. Contracept Fertil Sex 1993; 21(3):213-216.
18. Dijkman AB, Mol BW, van d, V, Bossuyt PM, Hogerzeil HV. Can hysterosalpingocontrast-sonography replace hysterosalpingography in the assessment of tubal subfertility? Eur J Radiol 2000; 35(1):44-48.
19. Lim CP, Hasafa Z, Bhattacharya S, Maheshwari A. Should a hysterosalpingogram be a first-line investigation to diagnose female tubal subfertility in the modern subfertility workup? Hum Reprod 2011; 26(5):967-971.
20. Reis MM, Soares SR, Cancado ML, Camargos AF. Hysterosalpingo contrast sonography (HyCoSy) with SH U 454 (Echovist) for the assessment of tubal patency. Hum Reprod 1998; 13(11):3049-3052.
21. Saunders RD, Shwayder JM, Nakajima ST. Current methods of tubal patency assessment. Fertil Steril 2011; 95(7):2171-2179.
22. Heikkinen H, Tekay A, Volpi E, Martikainen H, Jouppila P. Transvaginal salpingosonography for the assessment of tubal patency in infertile women: methodological and clinical experiences. Fertil Steril 1995; 64(2):293-298.
23. Emanuel MH, van Vliet M, Weber M, Exalto N. First experiences with hysterosalpingo-foam sonography (HyFoSy) for office tubal patency testing. Hum Reprod 2012; 27(1):114-117.
24. Emanuel MH, Exalto N. Hysterosalpingo-foam sonography (HyFoSy): a new technique to visualize tubal patency. Ultrasound Obstet Gynecol 2011; 37(4):498-499.
25. Strandell A, Waldenstrom U, Nilsson L, Hamberger L. Hydrosalpinx reduces in-vitro fertilization/embryo transfer pregnancy rates. Hum Reprod 1994; 9(5):861-863.
26. Zeyneloglu HB, Arici A, Olive DL. Adverse effects of hydrosalpinx on pregnancy rates after in vitro fertilization-embryo transfer. Fertil Steril 1998; 70(3):492-499.
27. Andersen AN, Yue Z, Meng FJ, Petersen K. Low implantation rate after in-vitro fertilization in patients with hydrosalpinges diagnosed by ultrasonography. Hum Reprod 1994; 9(10):1935-1938.
28. Bloechle M, Schreiner T, Lisse K. Recurrence of hydrosalpinges after transvaginal aspiration of tubal fluid in an IVF cycle with development of a serometra. Hum Reprod 1997; 12(4):703-705.
29. Mansour RT, Aboulghar MA, Serour GI, Riad R. Fluid accumulation of the uterine cavity before embryo transfer: a possible hindrance for implantation. J In Vitro Fert Embryo Transf 1991; 8(3):157-159.
30. Daftary GS, Kayisli U, Seli E, Bukulmez O, Arici A, Taylor HS. Salpingectomy increases peri-implantation endometrial HOXA10 expression in women with hydrosalpinx. Fertil Steril 2007; 87(2):367-372.
31. Donaghay M, Lessey BA. Uterine receptivity: alterations associated with benign gynecological disease. Semin Reprod Med 2007; 25(6):461-475.
32. Lu S, Peng H, Zhang H, Zhang L, Cao Q, Li R et al. Excessive intrauterine fluid cause aberrant implantation and pregnancy outcome in mice. PLoS One 2013; 8(10):e78446.
33. Mukherjee T, Copperman AB, McCaffrey C, Cook CA, Bustillo M, Obasaju MF. Hydrosalpinx fluid has embryotoxic effects on murine embryogenesis: a case for prophylactic salpingectomy. Fertil Steril 1996; 66(5):851-853.
34. Johnson N, van Voorst S, Sowter MC, Strandell A, Mol BW. Surgical treatment for tubal disease in women due to undergo in vitro fertilisation. Cochrane Database Syst Rev 2010;(1):CD002125.
35. Galen DI, Khan N, Richter KS. Essure multicenter off-label treatment for hydrosalpinx before in vitro fertilization. J Minim Invasive Gynecol 2011; 18(3):338-342.
36. Hitkari JA, Singh SS, Shapiro HM, Leyland N. Essure treatment of hydrosalpinges. Fertil Steril 2007; 88(6):1663-1666.
37. Inocencio G, Coutinho L, Maciel R, Barreiro M. Pregnancy after hydrosalpinx treatment with Essure. BMJ Case Rep 2013; 2013.

38. Matorras R, Rabanal A, Prieto B, Diez S, Brouard I, Mendoza R et al. Hysteroscopic hydrosalpinx occlusion with Essure device in IVF patients when salpingectomy or laparoscopy is contraindicated. Eur J Obstet Gynecol Reprod Biol 2013; 169(1):54-59.

39. Mijatovic V, Veersema S, Emanuel MH, Schats R, Hompes PGA. Essure hysteroscopic tubal occlusion device for the treatment of hydrosalpinx prior to in vitro fertilization-embryo transfer in patients with a contraindication for laparoscopy. Fertil Steril 2010; 93(4):1338-1342.

40. Mijatovic V, Dreyer K, Emanuel MH, Schats R, Hompes PGA. Essure(R) hydrosalpinx occlusion prior to IVF-ET as an alternative to laparoscopic salpingectomy. Eur J Obstet Gynecol Reprod Biol 2012; 161(1):42-45.

41. Omurtag K, Pauli S, Session D. Spontaneous intrauterine pregnancy after unilateral placement of tubal occlusive microinsert. Fertil Steril 2009; 92(1):393-397.

42. Ozgur K, Bulut H, Berkkanoglu M, Coetzee K, Kaya G. ICSI pregnancy outcomes following hysteroscopic placement of Essure devices for hydrosalpinx in laparoscopic contraindicated patients. Reprod Biomed Online 2014; 29(1):113-118.

43. Rosenfield RB, Stones RE, Coates A, Matteri RK, Hesla JS. Proximal occlusion of hydrosalpinx by hysteroscopic placement of microinsert before in vitro fertilization-embryo transfer. Fertil Steril 2005; 83(5):1547-1550.

44. Thebault N, Broux PL, Moy L, Vialard J. [Utilization of Essure(R) micro-insert for hydrosalpynx occlusion in infertile women]. J Gynecol Obstet Biol Reprod (Paris) 2012; 41(2):145-150.